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REVIEW ARTICLE

A Review on Therapeutic Role of Upadacitinib in Various Autoimmune Diseases

Milan Prabhakar, Sengar Yashwardhan Pratap Singh, Yogesh Joshi*
Department of Pharmacy Practice, School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Dehradun - 248001, Uttarakhand, India.
***Corresponding Author:** Yogesh Joshi
Email: yogeshjoshi1583@rediffmail.com

ABSTRACT
Autoimmune diseases (AD) affect a significant portion of the population and involve complex interactions between genetic and environmental factors. Upadacitinib, a newly approved JAK1 inhibitor, is showing promise in the treatment of AD and is undergoing clinical trials for various inflammatory disorders. Its pharmacokinetics demonstrate a high degree of solubility, a moderate protein binding, and a mostly CYP3A4-mediated metabolism. Strong CYP3A4 inducers and inhibitors should be monitored during treatment with Upadacitinib. Clinical studies have shown that it effectively treats Rheumatoid Arthritis both as monotherapy and in conjunction with other treatments, with a favourable benefit-risk profile. Upadacitinib has higher efficacy in treating Atopic Dermatitis (AD) symptoms and enhancing quality of life, both when used alone and in conjunction with topical corticosteroids. It exhibits promise as a strong JAK1 inhibitor in Psoriatic Arthritis (PsA), attaining main goals and relieving joint and skin symptoms. Research are being carried out regarding the best dosage methods. Upadacitinib represent a promising treatment for several immune-mediated inflammatory disorders.
Keywords: *Autoimmune, Upadacitinib, Rheumatoid Arthritis, Atopic Dermatitis, Psoriatic Arthritis*

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INTRODUCTION

Autoimmune diseases (AD) encompass over 70 distinct conditions that impact around 5% of the population in Western countries. These disorders exhibit considerable diversity in terms of the tissues they target, the age at which they manifest, and their responsiveness to immunosuppressive therapies. A common characteristic among AD is the involvement of both humoral and cellular immune responses in causing tissue damage. It is widely acknowledged that AD arises from complex interaction between genetic and environmental factors, many of which remain unidentified [1-4]. Upadacitinib, a newly approved JAK1 inhibitor by the US Food and Drug Administration (FDA), is used to treat adults with moderately to severely active Rheumatoid arthritis (RA) when methotrexate is ineffective or not tolerated.(5). It is now being examined in clinical trials for the treatment of different inflammatory disorders and is undergoing regulatory evaluation by several organisations worldwide. (6–9). Upadacitinib strongly targets JAK1 while showing lower potency against JAK2, JAK3, and TYK2 isoforms. The premise for developing Upadacitinib is that its heightened JAK1 potency could enhance RA treatment efficacy while minimizing interference with essential physiological JAK enzyme functions like hematopoiesis and immune responses. (10,11)

Pharmacokinetics of Upadacitinib

At clinically relevant doses, Upadacitinib is extremely permeable and highly soluble in the pH range of 1-7.5.(12). To plasma proteins, Upadacitinib is 52% bound. (6); As a result, displacement from plasma proteins is not anticipated to result in any meaningful interactions. Cytochrome P450 (CYP) enzyme 3A is the primary in vitro metabolizer of Upadacitinib, with CYP2D6 contributing in a negligible way.(12) The CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), as well as the

transporters P-glycoprotein (P-gp), didn't get inhibited or stimulated by Upadacitinib.(11) The metabolism of Upadacitinib may be influenced by potent inhibitors or enhancers of the enzyme CYP3A4.The Cmax and AUC were increased by 70% and 75%, respectively, following the injection of ketoconazole, a potent CYP3A4 inhibitor. Upadacitinib 15 mg once day should be used carefully in patients undergoing chronic treatment with potent CYP3A4 inhibitors, and when administered for an extended period, alternatives to potent CYP3A4 inhibitor drugs should be taken into consideration. administration of Rifampicin, a potent inducer of CYP3A4, resulted in a 50% and 60% reduction in Cmax and AUC respectively. As a result, if Upadacitinib is given along with strong CYP3A4 inducers, patients should be observed for changes in disease activity. (13,14) In phase 1 studies, the pharmacokinetics of Upadacitinib were assessed after immediate-release (IR) capsules were given to healthy participants in single doses ranging from 1 to 48 mg, multiple doses ranging from 3 to 24 mg twice daily to healthy participants, and 6 to 24 mg twice daily to participants with rheumatoid arthritis. The maximal Upadacitinib plasma concentration was reached after taking the Upadacitinib IR formulation within two hours of intake, following which plasma levels began to fall biexponentially. With twice-daily administration of the IR formulation, there was minimal Upadacitinib accumulation in plasma, and around 20% of the drug dose was unchangedly removed in urine.(15)

Table 1: Pharmacokinetics characteristics of Upadacitinib(14)

Characteristic	**Profile**
Absorption	2-4 hours for t_{max}.
Distribution	52% of protein binding
Metabolism	Primarily CYP3A4 and a small contribution of CYP2D6
Elimination	Predominantly in faeces (38%), and in urine (24%) as the parent substance that has not changed. Half-life of terminal elimination; average: 9–14 h.

Table 2: Dosing Recommendations of Upadacitinib based on Patient Characteristics(14)

Intrinsic factor	**Effect**	**Recommendation**
Age, gender, weight, race, and ethnicity	No clinically significant impact on Upadacitinib exposure	Based on these characteristics, Upadacitinib dose change is not necessary.
renal dysfunction	Upadacitinib exposure (AUC) increases with kidney impairment (18% in mild, 33% in moderate, 44% in severe). Peak concentration (Cmax) remains similar across kidney function levels.	No dose adjustment is needed in patients with mild or moderate renal impairment. However, for patients with severe renal impairment, the recommended dose is 15 mg once daily.
Hepatic impairment	Upadacitinib's area under the curve (AUC) was 28% greater in people with mild hepatic impairment and 24% higher in people with moderate hepatic impairment than it was in people with normal liver function. Upadacitinib's Cmax was constant with individuals who had normal liver function. The Cmax of Upadacitinib was 43% greater in people with mild hepatic impairment than it was in people with normal liver function. In patients with severe (Child-Pugh C) hepatic impairment, Upadacitinib was not examined.	Dose adjustment is not needed in the patients with a mild (Child–Pugh A)or a moderate (Child–Pugh B) hepatic impairment. In individuals with severe (Child-Pugh C) hepatic impairment, Upadacitinib should not be utilised.

Therapeutic Role of Upadacitinib

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is defined by persistent inflammation throughout the body, primarily affecting the synovial joints, which can ultimately result in bone erosion, deformities, and functional impairment. (16). RA is influenced by numerous cytokines in its pathophysiology, such as tumor necrosis factor (TNF)-α, interferon-γ, interleukin (IL)-1, IL-2, IL-6, IL-8, and IL-17. Within the cell, Janus kinases (JAKs) serve as intracellular enzymes responsible for transmitting signals from these cytokines or growth factors, participating in a variety of cellular processes like inflammatory responses, hematopoiesis, and immune

surveillance. The JAK family operates in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs). This phosphorylation, in turn, determines gene expression and cellular function. Specifically, JAK1 plays a crucial role in transmitting signals from inflammatory cytokines. (14,17) With the advancement of biologic and targeted synthetic disease modifying antirheumatic drugs (DMARDs) (bDMARDs and tsDMARDs, respectively), Over the past 20 years, RA treatments have evolved. As an outcome, Finally, early diagnosis is now possible for many patients and treated quickly, resulting in remission or minimal disease activity. However, there are still some patients who do not respond to current medications and require other treatment options in order to manage their health and lessen disease-related disability.(18,19) Janus kinase (JAK) enzyme activity is inhibited by JAK inhibitors (JAKi), which prevents cytokine signals from being transmitted and cytokine activities from occurring. Because of their mode of action, JAK inhibitors are potent therapeutic agents for the management of RA (17,20). Currently, tofacitinib, baricitinib, and, more recently, Upadacitinib and filgotinib have all received approval from the European Medicine Agency (EMA) for the treatment of RA. Baricitinib, tofacitinib and Upadacitinib have also received approval from the US Food and Drug Administration (FDA) for this indication.(21). Upadacitinib reduces the effects on natural killer cells and reticulocytes while preferentially inhibiting the activity of JAK1-dependent cytokines such as IL-6 and interferon-y. (14,21,22). A new drug application was presented to the FDA for Upadacitinib in December 2018. It has since received approval from both the FDA in August 2019 and the European Medicines Agency (EMA) in December 2019 for the treatment of RA, with the recommended dosage being 15 mg per day.(14). Upadacitinib has shown to be effective in treating RA in a variety of populations, resulting in a notable improvement in RA symptoms and signs as well as a reduction in the disease's radiographic progression and a significant improvement in patient-reported outcomes (PROs), such as pain and quality of life.(23) Similar to biologic disease-modifying antirheumatic medicines (bDMARDs), JAK inhibitors are being suggested as a potential treatment for rheumatoid arthritis (RA). (24), even though they are often used only when biological medications fail to work. The oral route and their effectiveness as monotherapy (i.e., without concurrent use of conventional synthetic (cs) DMARDs, particularly methotrexate (MTX)) have emerged as advantages over biological medicines.(25) Except for a few safety issues associated with JAKi, such as herpes zoster and blood creatine phosphokinase, which have been reported more frequently, the safety profile of this medication has undergone careful evaluation. The incidence of various side events appears similar to those seen with biological medicines. In observational studies, some potential issues, such as cardiovascular events, thrombosis, and cancer, will need to be the focus of long-term pharmacovigilance.(26)

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a commonly occurring inflammatory skin condition marked by severe itching and recurrent eczematous (eczema-like) lesions. The extreme itching brought on by AD has a substantial negative impact on the quality of life and sleep, especially in those with moderate to severe disease. Between 16% and 71% of patients are thought to be affected by this illness, with estimates varying by age group and location.(27–29) AD in adults may persist from childhood or may begin or reoccur in adulthood.(30,31) The occurrence of atopic dermatitis (AD) is not age-related and may develop at any point in life. Over the course of a patient's lifetime, AD symptoms may persist, resurface, or worsen (flare). Long-term persistence of the ailment is more prevalent in those with moderate-to-severe versions of the disease emphasizing the significance of good management and treatment techniques, especially for those who experience more severe symptoms. (32,33). AD is characterized by T-cell activation, both in the skin and the blood, but it is a complex and diverse disease. Different cytokine pathways, including the TH2 and TH22 pathways, are activated in AD. Furthermore, TH1 and TH17 cells tend to be involved in several disease subtypes. This diversity in the immune response highlights AD's multifaceted nature, with different individuals experiencing variations in the underlying immune mechanisms driving the condition. (34–36) Therefore, to achieve widespread efficacy, several cytokine axes may have to be targeted. Numerous cytokines involved in the pathogenesis of AD, such as TH2 cytokines (IL-4, IL-5, IL-13], IL-22, IL-31, IL-33, chemokines, thymic stromal lymphopoietin, and IFN-g, for example, act through intracellular signaling involving the Janus kinase (JAK) and signal transducer and activator of transcription pathways.(37) Preclinical studies exhibit a potential role for JAK inhibitors in the treatment of AD by demonstrating how the interruption of JAK1 signaling minimizes persistent itch through pathways involving TH2 cytokines, which may also directly stimulate neurons to elicit itching. The creation of novel drugs to interfere with this intracellular signaling pathway implicated in the immune responses associated with atopic dermatitis has been made possible by the increased understanding of the atopic dermatitis's pathogenesis and the function of Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways. JAK inhibitors are currently a major area of interest in atopic

dermatitis therapeutic research. Upadacitinib, an oral reversible small molecule that preferentially inhibits JAK1 over JAK2, JAK3, and tyrosine kinase 1, inhibits the JAK/STAT system and is now being studied for a few immune-mediated inflammatory illnesses. Reducing JAK2 and JAK3 inhibition may lessen side effects like anemia and infections.(38–41) Results from two ongoing phase 3 randomized, double-blind, replicate studies known as Measure Up 1 and Measure Up 2, have shown that both the 15 mg and 30 mg doses of Upadacitinib are superior to placebo (PBO). As monotherapy, both Upadacitinib dosages are well tolerated; they significantly reduce skin signs, itch, and pain; and improve the patient's health-related quality of life. Through 16 weeks, adults and adolescents with moderate-to-severe AD consistently show higher thresholds of skin improvement (i.e., >_90%/ >_100% improvement in Eczema Area and Severity Index [EASI-90/EASI-100]).(42) Systemic treatments are frequently combined with topical corticosteroids (TCS) to treat moderate-to-severe AD symptoms.(43)The primary results from a pivotal phase 3 clinical trial for AD demonstrate that the combination of Upadacitinib and TCS is well-tolerated and way more effective than a PBO + TCS in treating moderate-to-severe AD in both adolescents and adults. Patients getting either dose of Upadacitinib + TCS much more frequently show significant improvements, including more than 75% improvement in the Eczema Area and Severity Index (EASI-75), EASI-90, and EASI-100, as well as a validated Investigator's Global Assessment of AD (vIGA-AD) rating of clear or almost clear with at least a 2-grade improvement (vIGA-AD 0/1), when compared to those receiving PBO + TCS.(44,45) Results from the current phase 3, double-blind AD Up research show that Upadacitinib plus topical corticosteroid (TCS) has a favourable benefit-risk profile in individuals with moderate-to-severe atopic dermatitis. The patients received combination therapy consisting of Upadacitinib 15 mg + TCS, Upadacitinib 30 mg + TCS, and PBO + TCS. Upadacitinib 15 mg + TCS and Upadacitinib 30 mg + TCS remained effective until week 52 for all end goals. At week 52, 33.5% and 45.2% of patients receiving Upadacitinib 15 mg + TCS and Upadacitinib 30 mg + TCS, respectively, achieved EASI-75; 45.3% and 57.5%, respectively, experienced WP-NRS improvement >_4; and 50.8% and 69.0%, experienced vIGA-AD 0/1. Through 52 weeks, Upadacitinib +TCS was well tolerated; no additional significant safety concerns beyond those listed on the label were found. There were no recorded fatalities, and significant adverse cardiovascular events and venous thromboembolic incidents were infrequent. (46)

Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic systemic inflammatory condition characterized by a diverse range of clinical manifestations. It commonly involves joint inflammation and together with cutaneous psoriasis which affect up to 40% of psoriasis patients(47,48). Based on patient classification criteria and genetic variations by geographical area, PsA prevalence varies. For instance, 4%–30% of people worldwide have PsA, according to reports (49). With estimated pooled prevalence and incidence of 133/100,000 and 83/100,000, respectively, men and women are equally afflicted (50) . The JAK1-STAT3-STAT5 transcriptional pathway, which is linked to particular joint T cell populations, is expressed more frequently in PsA (51). The frequency of CD4+CD11a+CD45RO+IL-17+T cells can be controlled by a JAK inhibitor, according to studies. Furthermore, JAKi has been shown to reduce dendritic cell T cell-stimulatory capacity by suppressing type I interferon signalling as demonstrated by the induction of enthesitis in an A20meIKO animal model. JAKi can do this by inhibiting monocyte-derived dendritic cell differentiation through the production of reactive oxygen species and NOX5.(52–55) Patients with PsA are either primary or secondary non-responders to existing medications or are intolerant to them, highlighting the need for alternative targets with new mechanisms of action, such as Janus kinase inhibitors (JAK inhibitors) (56). UPA was recently granted approval by the EMA for the treatment of active PsA in patients who are intolerant to DMARDs or who have had an insufficient response to one or more DMARDs or conventional therapy (47). With little impact on the other isoforms, it is a powerful JAK1 inhibitor. IL-2, IL-6, IL-15, and -IFN are only a few of the cytokines that have an impact on the JAK1 receptor activation. Following the SELECT-PsA studies, which proved its safety and efficacy in treating PsA, the EMA approved it in January 2021 (48). Upadacitinib recently met the primary objective of an ACR20 response after 12 weeks in adult PsA patients who had not responded to conventional or biologic DMARDs in two phase 3 psoriatic arthritis clinical trials (SELECT-PsA 1 and 2) (57,58). Upadacitinib consumers in the Select PsA 1 study also reported superior results in terms of physical function (HAQ-DI at week 12) and skin symptoms (PASI-75 at week 16), with a higher percentage reaching minimum disease activity (MDA) after six months in contrast to the placebo group.(57). In the Select-PsA 2 study, the efficacy of the treatment was sustained for 56 weeks, showing the ongoing positive effects on both joint and skin disease. Additionally, dactylitis (inflammation of the fingers or toes) and enthesitis (inflammation of the regions where tendons or ligaments join to bones) both showed improvement. This

suggests that the medication was helpful in treating the symptoms of psoriatic arthritis (PsA), including enthesitis and dactylitis, over a long length of time in addition to regulating joint and skin symptoms (58). Across the spectrum of plasma concentrations reported in both SELECT PsA trials at 12 and 24 weeks, the 15 mg Upadacitinib dose showed the highest efficacy to adverse event ratio (59). Appropriate dose for instant release (IR) forms of between 1 and 48 mg and for extended release (ER) forms between 7.5 and 45 mg. A population pharmacokinetic investigation revealed that the former had a 76.2% lower oral bioavailability than the latter. (60–62).

CONCLUSION

JAK1 inhibitor Upadacitinib has been approved to treat a variety of autoimmune and inflammatory disorders, including psoriatic arthritis (PsA), rheumatoid arthritis (RA), and atopic dermatitis (AD). The article begins by highlighting the complexity of autoimmune disorders, emphasising the role of genetic and environmental variables, cellular and humoral immune responses, and the necessity for efficient therapies. Upadacitinib's pharmacokinetics are examined, highlighting its high solubility and permeability, modest plasma protein binding, and predominant CYP3A4 metabolism. Clinical trials on Upadacitinib has demonstrated promise as a rheumatoid arthritis therapeutic choice, especially for those who are not responsive to current medications. It is a favourable option because of its selective suppression of JAK1-dependent cytokines. The article also states the regulatory authorities' approval of it. Atopic dermatitis highlights the adverse impacts of this inflammatory skin condition on patients' quality of life as well as the effectiveness of JAK inhibitors like Upadacitinib in emphasising on the cytokine pathways related to AD. Clinical trials demonstrate its efficacy in improving skin symptoms and patient-reported outcomes. The article also emphasises Upadacitinib's acceptance as a therapy option for psoriatic arthritis patients that are not responding to conventional or biologic DMARDs. The SELECT-PsA studies have achieved their primary goals, increased physical function, and decreased skin complaints. In conclusion, Upadacitinib appears to be an efficient treatment for a variety of autoimmune and inflammatory disorders, with an emphasis on RA, AD, and PsA. In addition to its clinical effectiveness and safety profile, its specific suppression of JAK1-dependent cytokines highlights it in a favourable position to be a useful addition to the treatment choices for these difficult situations. To completely understand its role in the management of these disorders, however, additional research and long-term safety monitoring will be required.

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